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[Intervention Review]

Long-acting inhaled bronchodilators for cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is a life-limiting inherited condition which affects one in 2500 newborns in the UK and 70,000 children and adults worldwide. The condition is multifaceted and affects many systems in the body. The respiratory system is particularly affected due to a build up of thickened secretions and a predisposition to infection. Inhaled bronchodilators are prescribed for 80% of people with cystic fibrosis in order to widen the airways and alleviate symptoms. Both short- and long-acting inhaled bronchodilators are used to improve respiratory symptoms. Short-acting inhaled bronchodilators take effect in minutes and typically last for four to eight hours (muscarinic antagonists). Long-acting inhaled bronchodilators also take effect within minutes but typically last for around 12 hours and sometimes longer. This review is one of two which are replacing a previously published review of both long- and short-acting inhaled bronchodilators. However, due to the lack of research in this area, we do not envisage undertaking any further updates of this long-acting inhaled bronchodilators review.

Objectives

This review aims to evaluate long-acting inhaled bronchodilators in children and adults with cystic fibrosis in terms of clinical outcomes and safety. If possible, we aimed to assess the optimal drug and dosage regimen.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books.

Date of last search: 10 October 2017.

We also carried out a separate search of Embase and the reference lists of included trials. We searched clinical trials registries for any ongoing trials and made contact with pharmaceutical companies for any further trials.

Date of Embase search: 11 October 2017.

Selection criteria

Randomised or quasi-randomised parallel trials comparing long-acting inhaled bronchodilators (beta-2 agonists and muscarinic antagonists) with placebo, no treatment or a different long-acting inhaled bronchodilator in adults and children with cystic fibrosis.

Data collection and analysis

Both authors independently assessed trials for inclusion (based on title, abstract and full text). The authors independently assessed the included trials for quality and risk of bias and extracted data. Discrepancies were resolved by a third party.

Main results

The searches identified 195 unique references, of which 155 were excluded on title and abstract. We assessed the full texts of the remaining references, excluded 16 trials (28 references) and included four trials (12 references) in the review with 1082 participants.

One trial ($n = 16$) measuring the effect of beta-2 agonists reported an improvement in forced expiratory volume at one second (FEV_1) after treatment (at one month), but the trial was small with an unclear risk of bias so we judged the evidence to be very low quality. The trial did not report on participant-reported outcomes, quality of life or adverse events.

Three trials ($n = 1066$) looked at the effects of the muscarinic antagonist tiotropium at doses of 2.5 μg and 5.0 μg in both the short term (up to 28 days) and the longer term (up to three months). Only one of the trials reported the change in FEV_1 (L) after 28 days treatment and showed no significant difference between groups; with 2.5 μg tiotropium, mean difference (MD) -0.02 (95% confidence interval (CI) -0.13 to 0.09), or 5.0 μg tiotropium, MD 0.00 (95% CI -0.10 to 0.10) (moderate-quality evidence). All three trials of muscarinic antagonists provided data on adverse events which were found to differ little from placebo at doses of 2.5 μg , risk ratio (RR) 1.01 (95% CI 0.92 to 1.11) or 5.0 μg , RR 0.98 (95% CI 0.90 to 1.06). Very little participant-reported outcome data or quality of life data were available for analysis. Two of the trials were at low risk of bias overall whilst the remaining trial was at an unclear risk overall.

Authors' conclusions

Neither long-acting beta-2 agonists nor long-acting muscarinic antagonist bronchodilators demonstrate improvement in our primary outcome of FEV_1 . No difference was observed between intervention and placebo in terms of quality of life or adverse events. The quality of evidence for the use of beta-2 agonists was very low. The use of a long-acting inhaled bronchodilator may help to reduce the burden of treatment for people with cystic fibrosis as it is taken less often than a short-acting inhaled bronchodilator, but future trials would benefit from looking at the effects on our primary outcomes (spirometric changes from baseline, quality of life and adverse effects) in the longer term.

PLAIN LANGUAGE SUMMARY

Long-acting inhaled treatment to open up the airways in cystic fibrosis

Review question

We reviewed the evidence for the benefit of long-acting inhaled bronchodilators (treatment which opens up the airways often called "relievers") in people with cystic fibrosis.

Background

Cystic fibrosis affects many systems in the body, in particular how well the lungs work. There is a build-up of thickened, sticky mucus which makes breathing more difficult and makes people with cystic fibrosis more likely to get infections in their lungs. Short- and long-acting bronchodilators are prescribed for most people with cystic fibrosis to widen the airways and improve symptoms. This review partly replaces an earlier review of both short-acting and long-acting inhaled bronchodilators. However, due to the lack of research in this area, we do not plan to update this review of long-acting inhaled bronchodilators again.

Search date

The evidence is current to: 10 October 2017.

Trial characteristics

We included four trials in our review, with a total of 1082 people whose ages ranged from five months to 70 years. The trials included in the review looked at the effects of two different types of long-acting inhaled bronchodilator (beta-2 agonists e.g. salmeterol, and muscarinic antagonists e.g. tiotropium). The trials lasted between 28 days and 12 weeks.

Key results

The small trial of beta-2 agonists compared to placebo (no active medication) reported some improvement in lung function (forced expiratory volume at one second (FEV_1)) after treatment, but did not provide data we could analyse. They did not report on any side effects.

Only one of the three trials comparing tiotropium to a placebo reported on FEV_1 (measured in litres) and found little difference between treatment and placebo. Two of these trials reported on quality of life, but there was not enough evidence to comment on whether this improved or not. Three trials noted side effects, some of which were seen after treatment with tiotropium, but these symptoms were also seen in the group of people who were given placebo. Future trials would improve our knowledge if they measure side effects and quality of life in a more meaningful way.

Quality of the evidence

Only 16 people took part in the trial of the beta-2 agonist which only lasted for 28 days, which makes the results less reliable. The trials of muscarinic antagonists included 1066 people and the trials appeared to be well run. We don't think any design factors will have influenced the results in a negative way.

None of the trials ran for more than 12 weeks which makes it difficult to comment on the effects over a longer time period.

SUMMARY OF FINDINGS

Summary of findings 1. Beta-2 agonists versus placebo

Beta-2 agonists (salmeterol) compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: hospital inpatients

Intervention: long-acting beta-2 agonist (salmeterol)

Comparison: inhaled placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	salmeterol				
FEV ₁ : change from baseline Follow-up: 28 days	Children who received salmeterol twice a day showed a significant increase in FEV ₁ compared to children who received no treatment P < 0.05.		NA	16 (1)	⊕⊕⊕⊕ very low ^{1,2,3}	This trial included only children. The unit of measurement was not specified and only a P value was presented.
Participant-reported outcomes: quality of life (measured by CFQ-R) Follow-up: 12 weeks	Outcome not reported.					
Adverse events after tiotropium 5.0 µg Follow-up: 12 weeks	Outcome not reported.					
Pulmonary exacerbations Follow-up: N/A	Outcome not reported.					
Other measures of lung function Follow-up: N/A	Outcome not reported.					

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEF₂₅₋₇₅**: mid peak expiratory flow; **FEV₁**: forced expiratory volume in one second; **FVC**: forced vital capacity; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded twice due to risk of bias - this trial was at high risk of bias for blinding and at unclear risk of bias for four of the remaining five domains. The randomisation process and allocation concealment were unclear which was reflected in the risk of bias assessment.
2. Downgraded once due to imprecision - very small sample size from one trial.
3. Downgraded once due to indirectness - the trial only included children.

Summary of findings 2. LAMAs versus placebo

Inhaled tiotropium compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: inhaled tiotropium 2.5 µg to 5.0 µg

Comparison: inhaled placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tiotropium				
FEV ₁ : mean change from baseline (L) Follow-up: 28 days	The mean change in FEV ₁ (L) in the placebo group ranged from -0.02 to zero.	The mean change in FEV ₁ (L) after tiotropium 2.5 µg was 0.02 L lower than placebo (0.13 lower to 0.09 higher). There was no mean change in FEV ₁ (L) after tiotropium 5 µg (mean difference = zero (0.1 L lower to 0.1 L higher).	NA	34 (2.5 µg dose) 38 (5 µg dose) (1)	⊕⊕⊕⊕ low ^{1,2}	No significant difference was seen between tiotropium and placebo at either dose or in either age group.

Participant-reported outcomes: quality of life (measured by CFQ-R) Follow-up: 12 weeks	There were no differences in CFQ-R domain scores after 12 weeks of treatment with tiotropium.		NA	974 (2)	⊕⊕⊕⊖ low ³	No data were given for this outcome.
Adverse events after tiotropium 5.0 µg Follow-up: 12 weeks	755 per 1000	725 per 1000 (664 to 785)	RR 0.96 (0.88 to 1.04)	807 (2)	⊕⊕⊕⊕ high	A further trial reported adverse events over 28 days and so we have not combined the results. There were no significant differences between tiotropium at 2.5 or 5 µg and placebo with regard to adverse events (P = 0.97, P = 0.91 respectively).
Pulmonary exacerbations: participants reporting ≥1 pulmonary exacerbation during the trial period after tiotropium 5 µg Follow-up: 12 weeks	5 per 1000	3 per 1000 (2 to 6 per 1000)	RR 0.60 (0.32 to 1.12)	805 (2)	⊕⊕⊕⊖ moderate ⁴	The overall effect was not statistically significant.
Other measures of lung function: mean change from baseline in FEV ₁ AUC _{0-4h} (% predicted) after tiotropium 5.0 µg Follow-up: 12 weeks	The mean change in FEV ₁ ranged across placebo groups from -1.74% predicted to 0.87% predicted.	The mean change across both age groups in the tiotropium 5.0 µg groups was 2.59% higher (1.28 to 3.89) than placebo. The mean change across the 5 to ≤ 11 year age group was 1.97% higher (-0.57 to 4.52) than placebo. The mean change across the ≥ 12 year age group was 2.83% higher (1.37, 4.30) than placebo.	NA	770 (2)	⊕⊕⊕⊖ moderate ⁵	In both trials, a greater effect was seen in the ≥ 12 year age group than the younger age group.
Other measures of lung function: mean change from baseline in trough FEV ₁ (% predicted) after tiotropium 5.0 µg Follow-up: 12 weeks	The mean change in FEV ₁ ranged across placebo groups from -1.44% predicted	The mean change across both age groups in the tiotropium 5.0 µg groups was 1.81% higher (0.44 to 3.18) than placebo.	NA	772 (2)	⊕⊕⊕⊖ moderate ⁵	

to 0.72% predicted.	<p>The mean change across the 5 to ≤ 11 year age group was 0.88% higher (-1.76 to 3.53) than placebo.</p> <p>The mean change across the ≥ 12 year age group was 2.325 higher (0.81, 3.82) than placebo.</p>
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*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: cystic fibrosis questionnaire (revised); **CI**: confidence interval; **FEF₂₅₋₇₅**: mid peak expiratory flow; **FEV₁**: forced expiratory volume in one second; **FVC**: forced vital capacity; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to risk of bias as methods of blinding were not described.
2. Downgraded once due to imprecision due to a small sample size, low event rates and only one trial contributing data.
3. Downgraded twice due to imprecision as the data weren't presented and unclear risk of bias from lack of information.
4. Downgraded once due to imprecision due to low event rates.
5. Downgraded once due to indirectness: this is not a measure used routinely in the clinical area.

BACKGROUND

Please refer to the glossary for an explanation of terms used ([Appendix 1](#)).

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive inherited disease in white populations; it affects approximately 70,000 children and adults worldwide ([CF Foundation 2015](#)), with a rate of one in 2500 newborns in the UK ([Tobias 2011](#)). It was once considered a childhood disease, but with improvements in diagnosis and treatments, many people with CF are living well into adulthood. In 2012, data from the UK Cystic Fibrosis National Registry reported a median predicted survival of 43.5 years ([UK CF Trust 2014](#)).

CF is a multifaceted disease affecting the gastrointestinal, pulmonary and endocrine systems. The condition is caused by a faulty gene which encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). This protein regulates chloride, and so water, regulation across the cell membrane. Dysfunction leads to thickened, dehydrated mucus. In the lungs this results in chronic airway infection which can progress to bronchiectasis (damage to the airways), hypoxaemia (low oxygen levels) and hypercarbia (high carbon dioxide levels) ([O'Sullivan 2009](#)). Pulmonary disease causes considerable morbidity and accounts for almost 70% of CF-related deaths ([CF Foundation 2014](#)).

Adults and children with CF experience coughing, wheezing and shortness of breath due to reduced mucociliary clearance of the thickened mucus. Interventions to improve lung health include bronchodilators, hypertonic saline, dornase alfa, physiotherapy for airway clearance and antibiotics (oral, intravenous and aerosolised). In 2009, the Cystic Fibrosis Foundation Pulmonary Therapies Committee updated their guidelines for the maintenance of lung health and specifically looked at the evidence for each of these therapies ([Mogayzel 2013](#)). Bronchodilators are prescribed for over 80% of people with CF and many report that they help to alleviate the symptoms of wheezing and shortness of breath ([Colombo 2003](#)).

Concomitant asthma is also a problem for some individuals with CF and obtaining a diagnosis is often difficult. Obstruction of the airways and wheezing in CF share common features with asthma including airway mucosal oedema due to chronic inflammation and infection, obstruction of the airways by abnormally viscid secretions, stimulation of autonomic nerve fibres, airway smooth muscle contraction and airway collapse. In some individuals there may be a tendency to atopic asthma, which contributes to these symptoms ([Balfour-Lynn 2002](#)). There is no gold standard definition of asthma in children and the diagnosis is based on clinical symptoms (wheeze, breathlessness, chest tightness and cough) and variable airflow obstruction ([BTS 2016](#)). Airway hyper-responsiveness and airway inflammation are also described as components of the disease. Bronchodilator responsiveness is widely used in the diagnosis of asthma, but its role in CF is less clear cut due to the variability in lung function measures. In CF, the mechanisms of airway inflammation differ from asthma and result in progressive non-reversible airflow obstruction ([Balfour-Lynn 2002](#)).

Although CF and atopy, with or without asthma, may co-exist in some individuals, it is not known if these individuals will derive a greater benefit from the use of inhaled bronchodilators.

Description of the intervention

Both short-acting and long-acting inhaled bronchodilators are used to treat of CF pulmonary symptoms, to open the airways and help with airway clearance. They may also be prescribed to relieve symptoms attributable to CF asthma as an adjunct to physiotherapy, to help improve sputum clearance and to prevent bronchoconstriction-related symptoms during nebulised therapy. Short-acting and long-acting inhaled bronchodilators differ in their duration of action. Short-acting bronchodilators are used mainly for the relief of sudden attacks of breathlessness, they take effect within minutes and effects typically last four to six hours for beta-2 agonists and six to eight hours for muscarinic antagonists ([Cazzola 2012](#)). Long-acting bronchodilators are used for a longer-lasting effect and maintenance (as a preventer inhaler). Whilst they too take effect within a few minutes, the maximum bronchodilation may not occur for several hours and the duration of action is at least 12 hours ([Cazzola 2012](#)). The bronchodilation effect of a muscarinic antagonist bronchodilator, tiotropium lasts for over 24 hours ([Barnes 2000](#)).

This review will focus on long-acting bronchodilators, which can be classified into two types:

1. long-acting beta-2 agonists (e.g. salmeterol, formoterol);
2. long-acting muscarinic antagonists (LAMAs) (e.g. tiotropium, aclidinium).

While these different agents have the same clinical effect of causing the smooth muscle of the airways to relax, it is not appropriate to group them together as they have different properties and different modes of action. Both beta-2 agonists and muscarinic antagonists are delivered into the lungs via either a dry powder device or a metered dose inhaler (with or without the use of a large volume spacer to increase deposition in the lungs) or as an aerosol via a nebuliser (with or without additional oxygen), which usually requires a larger starting dose but delivers an equivalent dose to the lungs.

How the intervention might work

Both beta-2 agonists and muscarinic antagonists work by allowing the muscles in the lungs to relax, thus opening the airways and allowing increased air entry. Inhaled bronchodilators also have effects on mucociliary clearance ([Colombo 2003](#)).

Long-acting beta-2 agonists

A long-acting beta-2 agonist reaches the beta-2 receptors through the cell membrane. It has a lipophilic tail which binds to a receptor near the beta-2 adrenoceptor, so it stays bound for longer, and thus has a longer duration of action than short-acting beta-2 agonists. The actions of beta-2 agonists are mediated by cyclic adenosine monophosphate (cAMP). Increased intracellular cAMP increases the activity of cAMP-dependent protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular calcium concentrations. A lowered intracellular calcium concentration leads to smooth muscle relaxation and bronchodilation. Formoterol has an onset of action which is more

rapid; both formoterol and salmeterol cause bronchodilation which lasts for a minimum of 12 hours (Colombo 2003).

Long-acting muscarinic antagonists

Muscarinic antagonists affect the muscles around the bronchi and stop the muscles from tightening when they are irritated. Muscarinic antagonists bind to muscarinic receptors on airway smooth muscle and prevent action of acetylcholine via cyclic guanosine monophosphate (cGMP). This also results in reduced mucus secretion. They take effect in approximately 20 minutes and last for 24 hours, which means that these agents are only taken once a day for maintenance (ATS 2015).

Measurement of effect

Lung function in people with CF is commonly measured using spirometry measures such as forced expiratory volume in one second (FEV₁), peak expiratory flow rate (PEFR) and forced vital capacity (FVC). While FEV₁ remains the main measure of change caused by an intervention in CF, reversibility (a change in FEV₁ of 12% to 15%) is the standard by which change caused by bronchodilators is measured (Pellegrino 2005). These tests provide information for monitoring of lung function, but they require co-operation from the individual and a good technique. It has been noted that the results of such tests may be less reliable in children under the age of five to seven years (Kanengiser 1994).

Whilst the effect of bronchodilators can be measured by comparing the pre- and immediately post-dose lung function, with long-acting bronchodilators we are interested in the effect over time. We would be looking for an increase in FEV₁ for example, with every dose and a gradual increase in the average FEV₁ over time. Other effects include changes in quality of life (QoL), participant-reported symptoms, adverse events and exacerbations.

Why it is important to do this review

The updated CF Foundation Pulmonary Clinical Practice Guidelines report that there is insufficient evidence in favour of or against the use of inhaled muscarinic antagonists and the chronic use of beta-2 receptor agonists to improve lung function or quality of life (Mogayzel 2013). A previous Cochrane Review looked at the effectiveness of both short- and long-acting inhaled bronchodilators for CF (Halfhide 2005). More than a decade on from this original review, it is important to update this review and search for more recent trials of long-acting inhaled bronchodilators to provide a clearer picture of their efficacy in terms of lung function but also in terms of their effect on QoL and adverse events.

Following the initial version of this review focussing on long-acting inhaled bronchodilators it has been agreed not to undertake any further updates due to the lack of research in this area.

OBJECTIVES

This review aims to evaluate long-acting inhaled bronchodilators in children and adults with CF in terms of clinical outcomes and safety. If possible, we aimed to assess the optimal drug and dosage regimen.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We assessed quasi-RCTs on their merit using the Cochrane risk of bias tool; if the method of allocation was described (e.g. alternate allocation, date of birth or medical record number) and both reviewer authors were satisfied that the groups were similar at baseline, we included them.

In a post hoc change we excluded cross-over trials; due to the carry-over effects of long-acting medication, it is not possible to ensure that the groups are the same at baseline.

We included trials published as full texts. If there was only an abstract available for a trial, we included it if results were presented. If no results were presented in either the abstract or on any trials registry sites, we classified this trial as 'Awaiting assessment' until more information was available. Similarly with unpublished trials, if a trial met our inclusion criteria and quality assessment, then we included it.

Types of participants

Children and adults with CF diagnosed by sweat test or genetic testing, with all stages and severity of lung disease and with or without concomitant asthma.

Types of interventions

Long-acting inhaled bronchodilators delivered via any device and at any dose, frequency or duration. For this review we considered the term 'inhaled' to include the use of pressurised metered dose inhalers (MDIs) with or without a large-volume spacer, dry powder devices and nebulisers. We included both types of long-acting bronchodilators which have a duration of action of at least 12 hours:

- beta-2 agonists, e.g. salmeterol, formoterol;
- muscarinic antagonists, e.g. tiotropium, aclidinium.

We did not consider combined inhalers (with inhaled steroids or another bronchodilator) or short-acting inhaled bronchodilators (e.g. salbutamol, ipratropium bromide).

The comparator was an inhaled placebo, another long-acting bronchodilator (or the same drug at a different dose) or usual treatment. It is possible that usual treatment may include a short-acting bronchodilator and therefore participants randomised to the long-acting bronchodilator may also be taking a short-acting bronchodilator. We took this into consideration by looking at the inclusion and exclusion criteria of individual trials.

Types of outcome measures

Primary outcomes

1. Change in FEV₁ from baseline (L and per cent (%) predicted)
2. Participant-reported outcomes including QoL using standardised and validated QoL scores (e.g. CFQ-R (Quittner 2009)) and symptom scores (e.g. Respiratory and Systemic Symptoms Questionnaire (RSSQ), Respiratory Symptom Score (RSS) (Goss 2007))
3. Adverse effects (especially those associated with long-acting inhaled bronchodilators i.e. for beta-2 agonists tremor, nervous

tension, headache, peripheral dilatation and palpitation, increased heart rate, dry mouth, increased wheeze and shortness of breath; for LAMAs dry mouth, gastrointestinal motility disorder (constipation and diarrhoea), nausea, gastro-oesophageal reflux disease, dysphagia, tachycardia)

- a. frequency of adverse effects
- b. severity of adverse effects, e.g. mild or moderate or severe (where it has been reported)

Secondary outcomes

1. Number of exacerbations of respiratory symptoms as defined by
 - a. individual clinicians or the use of a scoring system such as the RSSQ, or both
 - b. the need for hospitalisation or antibiotics or both
2. Time to first exacerbation
3. Other measures of lung function
 - a. peak expiratory flow rate (PEFR) (L per minute and % predicted)
 - b. measures of bronchial hyper-responsiveness and bronchodilator responsiveness, e.g. reversibility, methacholine challenge or equivalent (histamine or mannitol), exercise testing
 - c. forced expiratory flow between 25% and 75% of expiratory flow (FEF₂₅₋₇₅) (L per second and % predicted)
 - d. forced vital capacity (FVC) (L and % predicted)
 - e. any other measurements of lung function that are relevant, e.g. trough FEV₁, lung clearance index (LCI) and area under the curve (AUC)

Search methods for identification of studies

We did not restrict the searches by language, year or publication status.

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: bronchodilator AND (inhaled OR *stated).

The Cystic Fibrosis Trials Register has been compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the *Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective Handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work has been identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group [website](#).

Date of the latest search: 10 October 2017.

We also carried out a separate search of Embase from inception using the search terms cystic fibrosis AND bronchodilator AND inhaled ([Appendix 2](#)).

Date of the latest search: 11 October 2017.

Grey literature

We searched Open Grey using the search terms "bronchodilator*" AND "cystic fibrosis" (<http://www.opengrey.eu/>). There were no resulting papers to add to the main search results for screening by two reviewer authors.

Date of the latest search: 16 October 2017.

Clinical trial registries

We searched the clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/en/) for any ongoing and or unpublished trials using the terms " bronchodilator" and "cystic fibrosis". We also included drug names (formoterol, salmeterol, tiotropium and alcidium) to increase sensitivity of the search where trials may only list the drug name.

Date of the latest search (Clinical Trials.gov; ISRCTN): 11 October 2017.

Date of latest search (ICTRP): 13 November 2017.

We searched the AstraZeneca Clinical Trials Website (astrazenecagrouptrials.pharmacm.com/ST/Submission/Search) on 16 October 2017.

Searching other resources

Reference Lists

We searched reference list of all included trials to identify any further relevant trials.

Date of the latest search: 25 August 2016.

Correspondence

We contacted the pharmaceutical companies Allen & Hanburys (A&H) (which is part of GlaxoSmithKline (GSK)) and Novartis for information on any unpublished trials or relevant research.

Date of correspondence: 02 April 2016.

Where papers were only in abstract form, we contacted the author to try and obtain a full paper or more information on the trial. Date of contact (Turchetta) 12 July 2017.

Data collection and analysis

Selection of studies

Once we had the complete list of identified references, one review author (SS) checked for duplicates and removed them. Both authors (SS and CE) then reviewed all titles and abstracts and discarded references which clearly didn't meet the inclusion criteria. We attempted to resolve any disagreements by discussion, but where a decision could not be reached then we asked the managing editor of the review group to mediate until we could reach a final decision. Once we had discarded trials on the basis of title and abstract, we obtained full copies of the remaining references and screened these using a standardised screening form customised for this review.

We considered trials in any language, but all the trials identified were in English. We have presented the results of the searches in a flow chart ([Figure 1](#)).

Figure 1. Study flow diagram.

Data extraction and management

Both review authors independently extracted data using a specially designed data extraction form developed by the Cochrane Cystic Fibrosis and Genetic Disorders Review Group and adapted to this review. We collected data on:

- participant characteristics;
- trial characteristics and trial design;
- intervention and comparator;
- outcome data - we reported data for each outcome separately.

One author (SS) checked the independent data extraction forms for discrepancies and where these could not be resolved by discussion, the Managing Editor of the review group (NJ) arbitrated.

One author (SS) entered the doubly extracted data into Review Manager software for analysis (RevMan 2014). We entered and presented data for beta-2 agonists and muscarinic antagonist bronchodilators separately due to their different properties and modes of action. We planned to carry out the following comparisons:

- beta-2 agonists versus placebo or usual treatment or another beta-2 agonist;
- LAMAs versus placebo or usual treatment or another muscarinic antagonist agent; and
- beta-2 agonists versus LAMAs.

We planned to present outcome data at up to seven days, over seven days and up to 28 days, over 28 days and up to three months, over three months and up to six months, over six months and up to a year and annually thereafter.

Assessment of risk of bias in included studies

We used the risk of bias tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias across six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias) (Higgins 2011). Both authors assessed the included trials for risk of bias independently and we compared our results. Again, any discrepancies were resolved by discussion and where this did not lead to agreement, we involved a third person (Managing Editor of the review group (NJ)).

Where the trial described the methods of randomisation and allocation, including the concealment of the allocation sequence from the researchers, and both reviewers deemed these to be adequate, then we ranked the trial as having a low risk of bias for this domain. Where these were inadequate, we ranked the trial as being at a high risk and where it was unclear from the description given, then we ranked it as having an unclear risk of bias.

Similarly for blinding, we looked at the method used and who was blinded to determine the risk of bias. We deemed trials to have a low risk of bias if it was double blinded with participants, investigators and outcome assessors being blind to the treatment that was allocated. Where a trial was only partially blinded, the risk of bias was considered to be higher and where the trial was unblinded, the risk was deemed to be high.

We extracted information on missing data and how the investigators recorded participant withdrawals and loss to follow-

up. We also looked at whether missing data were equally distributed between the intervention and control groups. If both review authors agreed that missing data had been accounted for adequately, then we judged the trial to be at a low risk of bias. We recorded the trial as having a high risk of bias if the missing data were not reported adequately and recorded it as having an unclear risk of bias if we were unable to see how the missing data had been reported. Two authors assessed each included trial to determine whether the investigators used an intention-to-treat (ITT) analysis and again, once we reached an agreement, we ranked the trials as being at a high, low or unclear risk of bias.

If the trial investigators reported all outcomes in the paper, the two review authors recorded a low risk of bias from selective reporting. If there were outcomes stated as being measured where the investigators do not report results, the review authors ranked the paper as being at high risk. If it was unclear to both review authors whether all outcomes were reported, then we stated this and ranked it as unclear for this domain. We searched for trial protocols to be able to assess outcome reporting. If the protocol could be found, we assessed outcome reporting based on a comparison between the methods section of the full published paper and the results section.

Both review authors looked for any other potential sources of bias in the included trials and recorded what they found. If neither author could find any other source of bias, then we ranked the trial as having a low risk for this domain and high risk if the opposite was true.

We presented the results of the risk of bias assessment both individually and in a summary table.

Measures of treatment effect

We reported measures of treatment effect for each outcome and for each type of long-acting bronchodilator separately.

For dichotomous data (adverse effects), we calculated a pooled estimate of the treatment effects for each outcome across trials using risk ratio (RR) and 95% confidence intervals (CIs) where appropriate.

For continuous data (FEV₁, FVC, FEF₂₅₋₇₅%, PEFR, LCI, QoL and symptom scores) we recorded the mean change and standard deviation (SD) from baseline for each group. We calculated a pooled estimate of treatment effect using the mean difference (MD) and 95% CIs where it was possible to combine trial outcome data. It was not possible to combine data from trials where the outcomes and time points were different. In future updates where trials use different units of measurement or measurement scales for reporting the same outcome (e.g. QoL) we will use the standardised mean difference (SMD) to report the results. Where trials reported only a pre-intervention mean (SD) and post-intervention mean (SD) then we calculated the mean change but not the SD of the change. These results have been reported narratively.

For FEV₁ we looked for a change of over 12% for a meaningful effect and a change of over 15% in FEF₂₅₋₇₅ (Barreiro 2004).

No time-to-event data was reported in any of the trials but if this type of data is reported in future trials, we will express the

intervention effect as a hazard ratio (HR) with 95% CIs using the generic inverse variance method.

Unit of analysis issues

In multi-arm trials, where the data fell into more than one comparison, each treatment arm was analysed separately against placebo and where appropriate included in a meta-analysis. In future updates, if the two active treatment arms are of the same type of long-acting bronchodilator, but employ a different drug or dose, we will combine them against the placebo arm to look at the effect of the different type of long-acting bronchodilator rather than an individual drug.

Cross-over trials are not eligible for inclusion due to the carry-over effects of long-acting medication.

We planned to carry out a subgroup analysis to look at the effect of individual drugs if there was heterogeneity between trials looking at different types of long-acting bronchodilator ([Subgroup analysis and investigation of heterogeneity](#)).

Dealing with missing data

We attempted to request additional data from the trial author(s) if there were insufficient data in the published paper or uncertainty about data we were able to extract from the included trials.

We assessed the extent to which trial authors have employed an ITT analysis and we reported the numbers of participants who dropped out of each arm of the trial, where possible.

Assessment of heterogeneity

Where there were trials reporting the same outcomes which we are able to include in a meta-analysis, we assessed the level of heterogeneity using the I^2 statistic. We looked at the overlap of the CIs on the forest plots to gauge the significance of the I^2 value.

We based our definitions of different levels of heterogeneity on the levels described in the *Cochrane Handbook for Systematic Reviews of Interventions*:

- low (might not be important) = 0% to 40%;
- moderate = 30% to 60%;
- substantial = 50% to 90%; and
- considerable = 75% to 100%.

The *Cochrane Handbook for Systematic Reviews of Interventions* states that this is a rough guide because the importance of inconsistency depends on several factors ([Higgins 2011](#)).

Assessment of reporting biases

We planned to generate a funnel plot to attempt to identify any publication bias in the included trials ([Higgins 2011](#)); however, there were less than 10 included trials and therefore, insufficient trials to conduct this analysis. We attempted to identify any selective reporting in the included publications, by comparing the trial protocols with the final papers and by careful examination of the trial publications and consideration of reporting of both positive and negative effects of the intervention. Where trial protocols weren't available, we compared the outcomes reported in the results section against the methods section of the paper. We extracted information on the sponsors, sources of funding and

competing interests of the authors to determine the role of external bias being introduced. To minimise publication bias, we searched trial registries and contacted pharmaceutical companies for any unpublished data.

Data synthesis

Where we were able to combine trials in a meta-analysis, we used the data from the selected trials to generate forest plots using the Review Manager software ([RevMan 2014](#)). We carried out separate meta-analyses for the two different types of long-acting bronchodilators. We examined the level of heterogeneity to determine which type of analysis model to use. If there was low heterogeneity (less than 40%) then we used a fixed-effect model and if the I^2 statistic was greater than 40% then we used a random-effects model to summarize the data.

Subgroup analysis and investigation of heterogeneity

If there was greater than 40% heterogeneity in the included trials, we planned to undertake subgroup analyses to look at:

- severity of lung disease (based on a classification by Pellegrino using values for FEV₁ % predicted, we will use the following definitions: mild (over 70%); moderate (60% to 69%); moderately severe (50% to 59%); severe (35% to 49%); very severe (below 35%) ([Pellegrino 2005](#)));
- presence of asthma;
- presence of measured airway reversibility (based on reversibility or methacholine challenge or exercise testing);
- age (children under 18 versus adults aged 18 or over);
- the effect of individual drugs.

There were insufficient trials with comparable outcomes to be able to carry out subgroup analyses of severity of lung disease, presence of asthma or presence of measured airway reversibility. As there was only one drug in each of the comparisons it wasn't possible to carry out a subgroup analysis on the effect of individual drugs.

It was possible to look at the effect of age for two of the trials looking at tiotropium.

Sensitivity analysis

Where we have carried out a meta-analysis, we planned to carry out sensitivity analyses to look at the effect of the risk of bias findings and to look at the effect of adding in and taking out trials where there was high risk of bias. This was not possible due to there not being enough trials included in a meta-analysis.

Summary of findings and assessment of the certainty of the evidence

We have reported summary of findings information where there was at least one trial assessing our chosen outcomes for the comparison of beta-2 agonists versus control and muscarinic antagonists versus control and for the outcomes:

- change in FEV₁ from baseline;
- participant-reported outcomes (QoL);
- adverse events;
- pulmonary exacerbations;
- other measures of lung function.

For each outcome we have reported the illustrative risk with and without the intervention, magnitude of effect (RR or MD), numbers of trials and participants addressing each outcome and a grade of the overall quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) with comments ([Schunemann 2006](#)).

We have created separate tables for each separate comparison we present.

RESULTS

Description of studies

Results of the search

The searches identified 195 unique references which were filtered by two authors (SS, CE) on title and abstract resulting in 40 references (20 trials) which were screened on full text. We have included four trials (12 references) with 1082 participants which met our inclusion criteria and have excluded 16 trials (28 references) with reasons ([Excluded studies](#)). No ongoing trials were identified and no trials are awaiting classification (see PRISMA flow chart [Figure 1](#)).

Included studies

We identified four trials (12 references) which were eligible for inclusion; one trial examined the effects of the beta-2 agonist salmeterol ([Turchetta 1998](#)) and the remaining three trials examined the effects of the muscarinic antagonist tiotropium ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). One trial was reported only in abstract form ([Turchetta 1998](#)), whilst the remaining three trials were reported as full-text articles ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). The characteristics of the included trials are presented in the tables ([Characteristics of included studies](#)).

Beta-2 agonists

One trial (16 participants) looked at the effects of inhaled long-acting beta-2 agonists ([Turchetta 1998](#)).

Trial design

This trial was of parallel design and was carried out over one month ([Turchetta 1998](#)). The trial report did not state where it was conducted, although all the authors listed on the abstract were affiliated to the same children's hospital in Italy ([Turchetta 1998](#)).

Participants

The trial had small numbers of participants with only 16 young people being included ([Turchetta 1998](#)). The participants were children with a mean (SD) age of 13.9 (3.1) years and a range of 10 to 17 years. The gender split was weighted towards males (68.7%) ([Turchetta 1998](#)). Disease severity at baseline was reported as a mean (SD) FEV₁ % predicted at baseline of 72% (19) ([Turchetta 1998](#)). The trial did not state whether the participants had asthma.

Interventions

The intervention in this trial was the beta-2 agonist, salmeterol which was given twice daily (two puffs) (actual dose not stated) and the comparator used was no treatment ([Turchetta 1998](#)).

Outcomes

The trial reported on change from baseline in FEV₁ to end of treatment (a month of treatment), although no data (only a significance level) were reported in the [Turchetta](#) abstract. They also reported on FVC but again, only the significance level was given. The trial did not report on adverse events or participant-reported outcomes, pulmonary exacerbations or any other measures of lung function ([Turchetta 1998](#)).

Muscarinic antagonists

Three trials examined the effects of long-acting muscarinic antagonist bronchodilators ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). The three trials with their associated references reported on phase I ([Konstan 2015](#)), phase II ([Bradley 2014](#)) and phase III ([Ratjen 2015](#)) of a randomised, multicentre trial carried out across Europe, USA and Australia.

Trial design

The three trials were parallel in design ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)), one of these being a step-wise dose escalation trial ([Konstan 2015](#)), and were measured over one month ([Konstan 2015](#)) and 12 weeks ([Bradley 2014](#); [Ratjen 2015](#)).

Participants

The three trials had numbers of participants ranging from 92 ([Konstan 2015](#)) to 510 ([Bradley 2014](#)) and included both children and adults with an age range of five months (0.4 years) to 70.5 years ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). The proportion of male participants ranged from 54% ([Bradley 2014](#)) to 56% ([Ratjen 2015](#)). Disease severity at baseline was measured in all three trials as % predicted FEV₁. Mean (SD) FEV₁ % predicted ranged from 89.8% (17.8%) ([Ratjen 2015](#)) to 98.7% (12.8%) ([Konstan 2015](#)) in the participants aged 11 or younger; and 68.8% (23.3%) to 74.4% (21.4%) ([Konstan 2015](#)) in participants aged 12 or over. None of the trials stated whether the participants had asthma.

Interventions

All three trials examined the effects of tiotropium bromide in varying doses and schedules. The dose administered ranged from 2.5 µg ([Bradley 2014](#); [Konstan 2015](#)) to 10.0 µg ([Konstan 2015](#)) via Respimat Soft mist inhaler. The [Bradley](#) trial administered a single dose of tiotropium at one time point ([Bradley 2014](#)), one trial administered treatment twice a day ([Ratjen 2015](#)) and the third trial looked at the effects of a single dose and multiple doses (once daily for 28 days) within the same trial report ([Konstan 2015](#)). In this review we only included the multiple dose trial. In both the [Bradley](#) and [Ratjen](#) trials, participants continued their regular treatment which in some cases included a short-acting bronchodilator. In the [Bradley](#) trial 61.3 % of the placebo group were taking short-acting bronchodilators, 54.2 % of the 2.5 µg group and 63.1 % of the 5 µg group ([Bradley 2014](#); [Ratjen 2015](#)).

Outcomes

Only one of the three trials reported on a measure of FEV₁ to examine the effectiveness of LAMAs on lung function. The trial reported the change from baseline in mean (SD) FEV₁ L to the end of the 28-day trial period ([Konstan 2015](#)). Two trials measured QoL using CFQ-R domain scores ([Bradley 2014](#); [Ratjen 2015](#)).

All three trials measured and reported on adverse events including drug-related adverse effects but for differing lengths of time (Bradley 2014; Konstan 2015; Ratjen 2015). Two trials reported on the number of exacerbations in the trial period; both trials recorded the number of participants experiencing one or more exacerbations (Bradley 2014; Ratjen 2015).

None of the trials reported on the need for hospitalisation and/or antibiotics, or time to first exacerbation.

Two trials reported other measures of lung function (Bradley 2014; Ratjen 2015). For both of these trials, FEV₁ AUC_{0-4h} (% predicted and L) was the primary endpoint and they also measured trough FEV₁, FVC AUC_{0-4h}, and trough FVC.

Excluded studies

We excluded 16 trials (28 references) from the review because they did not meet the inclusion criteria. Brief descriptions of the excluded trials and reasons for exclusion are given in the tables (Characteristics of excluded studies). After a post hoc change to the protocol we excluded cross-over trials due to the carry-over effect of long-acting medication leading to risk of bias. Three trials were excluded on this basis and have been described in an additional table (Table 1) (Keir 2007; Rodrigues 2008; Salvatore 2002).

Nine trials did not report on the effects of a long-acting bronchodilator (Dodd 2005; Konstan 2014; Nikolaizik 1996a; Orlik 2002; Regelman 1990; Serisier 2007; Weintraub 1989; Wiebicke 1990; Ziebach 2001). Konstan studied the effect of BIL 284 BS,

a LTB₄ receptor antagonist which was taken orally rather than inhaled (Konstan 2014). Two trials reported on the effects of inhaled antibiotics, one trial looked at nebulised tobramycin (Nikolaizik 1996a) and the other at parenteral antibiotics compared to placebo (Regelman 1990). Three trials examined the effects of short-acting beta-2 agonists. Dodd and Orlik looked at salbutamol (Dodd 2005; Orlik 2002) whilst Serisier looked at the effects of albuterol (Serisier 2007). Three trials examined the effects of the short-acting muscarinic antagonist bronchodilator ipratropium bromide (Weintraub 1989; Wiebicke 1990; Ziebach 2001); with the latter also looking at salbutamol and a combination of ipratropium and salbutamol.

Two trials looked at the effects of a long-acting bronchodilator, but the comparator was a short-acting bronchodilator rather than placebo, no treatment or another long-acting bronchodilator (Hordvik 2002; Turchetta 1996). An earlier Hordvik trial looked at the effect of a long-acting beta-2 agonist in a three-arm cross-over trial. There was no washout period in between the cross-over of treatments and we have since excluded cross-over trials (Hordvik 1999).

The remaining paper identified was a review rather than a trial and was excluded on this basis (Nielsen 2006).

Risk of bias in included studies

The risk of bias was assessed by both authors for all trials included in the review and the details are given in the table (Characteristics of included studies) and summarised below (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Bradley 2014							
Konstan 2015							
Ratjen 2015							
Turchetta 1998							

Allocation

Sequence generation

All four of the included trials were described as randomised with three of them giving full details of the randomisation process and

being deemed to be at low risk of bias (Bradley 2014; Konstan 2015; Ratjen 2015). Bradley and Ratjen randomised participants using a computer-generated randomisation schedule and in the Konstan trial participants were randomised via a third-party telephone interactive voice randomisation system. The remaining trial did not

describe the randomisation process and was deemed to have an unclear risk of bias (Turchetta 1998).

Allocation concealment

Allocation of participants was concealed in the Bradley trial where medication was prepared and coded by Boehringer Ingelheim in a blinded fashion (Bradley 2014). Allocation was also adequately concealed in the Konstan trial, where allocation was made by a third-party telephone randomisation system (Konstan 2015), and in the Ratjen trial, where participants were allocated in a 1:2 placebo:active ratio in a blinded fashion (Ratjen 2015). It was unclear whether allocation was concealed for the Turchetta trial as it was not described in the trial documentation (Turchetta 1998).

Blinding

Two trials were deemed to be at low risk of bias from blinding as they were stated to be double-blind and the methods of blinding were well-described (Bradley 2014; Ratjen 2015). In the Bradley trial, Boehringer Ingelheim prepared and coded the medication in a blinded fashion and provided all trial supplies (Bradley 2014). Similarly, in the Ratjen trial all the trial medication was prepared and coded in a blinded fashion (Ratjen 2015). One trial was described as double-blind but provided no further details of which parties were blinded or methods, so the risk of bias was deemed as unclear (Konstan 2015). The Turchetta trial did not describe blinding but stated that the comparator was no treatment. It is therefore likely that the participants were aware of the group they had been assigned to and the trial was deemed to be at high risk of bias (Turchetta 1998).

Incomplete outcome data

One trial did not describe withdrawals and was judged to have an unclear risk of attrition bias (Turchetta 1998). The remaining three trials all reported withdrawals, but numbers of withdrawals were low and reasons were given so they were judged as being at low risk of bias (Bradley 2014; Konstan 2015; Ratjen 2015).

Selective reporting

Three of the four included trials were deemed to be at low risk of selective reporting bias and although the protocol was only available for one trial (Bradley 2014), supplementary documentation was available online for the other two trials (Bradley 2014; Ratjen 2015). Furthermore, clinical trial registration documentation was available for three trials (Bradley 2014; Konstan 2015; Ratjen 2015). For the trial where there was no protocol or supporting information, the outcomes reported were checked against those stated in the methods; one of the three primary outcomes listed in the methods (FVC) was not reported in the results and so this trial was considered to be at unclear risk of selective reporting bias (Turchetta 1998).

Other potential sources of bias

None of the trials were given a low-risk rating for other potential sources of bias. Three of the trials were judged to have an unclear risk of bias based on the fact that they were funded by the pharmaceutical company Boehringer Ingelheim (Bradley 2014; Konstan 2015; Ratjen 2015). In two trials Boehringer Ingelheim were involved in trial design, data collection and analysis, interpretation of data, preparation of the manuscript and decision to publish

(Bradley 2014; Ratjen 2015); in the third trial they employed some of the authors (Konstan 2015).

One trial was only published in abstract form and there was therefore insufficient information to be able to identify other potential sources of bias (Turchetta 1998).

Effects of interventions

See: [Summary of findings 1 Beta-2 agonists versus placebo](#); [Summary of findings 2 LAMAs versus placebo](#)

Beta-2 agonists versus placebo or usual treatment or another beta-2 agonist

Only one trial (n = 16) is included in this comparison (Turchetta 1998). A summary of the main findings is provided in the summary of findings table ([Summary of findings 1](#)).

Primary outcomes

1. Change in FEV₁ from baseline (L and % predicted)

a. medium term (7 to 28 days)

Turchetta reported that children who received salmeterol twice a day via a spacer showed an increase in FEV₁ (unit of measurement not specified) (P < 0.05) compared to children who received no treatment; but no data were presented (Turchetta 1998).

GRADE: the quality of this evidence was deemed to be very low.

2. Participant-reported outcomes (including QoL and symptom scores)

The included trial did not present any participant-reported outcomes.

3. Adverse effects

The included trial did not report on adverse events.

Secondary outcomes

1. Number of exacerbations of respiratory symptoms

The included trial did not report on this outcome.

2. Need for hospitalisation or antibiotics or both

The included trial did not report on this outcome.

3. Time to first exacerbation

The included trial did not report on this outcome.

4. Other measures of lung function

a. PEFR (L per minute and % predicted)

The included trial did not report on this outcome.

b. measures of bronchial hyper-responsiveness and bronchodilator responsiveness

The included trial did not report on this outcome.

c. FEF₂₅₋₇₅ (L per second and % predicted)

i. medium term (7 to 28 days)

The trial did not report FEF₂₅₋₇₅ in the medium term.

d. FVC (L and % predicted)

Although the trial authors stated that FVC was measured, no results were reported.

e. any other measurements of lung function that are relevant

No other measures of lung function were reported for this comparison.

Muscarinic antagonists versus placebo or usual treatment or another muscarinic antagonist

Three trials (n = 1066) were included in this comparison (Bradley 2014; Konstan 2015; Ratjen 2015). A summary of the main findings is provided in the table (Summary of findings 2).

Primary outcomes**1. Change in FEV₁ from baseline (L and % predicted)**

Only one of the three trials reported a change in FEV₁ (L) from baseline after treatment with tiotropium (Konstan 2015).

a. medium term (7 to 28 days)

This multiple-dose trial compared two doses of tiotropium and placebo in two age groups, a younger age group (5 years up to 11 years) and an older age group (12 years and over) and reported data after 28 days of treatment for FEV₁ (L). Analysis of results from participants receiving 2.5 µg of tiotropium or placebo showed no significant difference between the groups in the younger or older age group, MD -0.02 (95% CI -0.13 to 0.09) (Analysis 1.1) (Figure 3). Likewise, there was no significant difference between groups allocated to 5 µg of tiotropium or placebo, MD 0.00 (95% CI -0.10 to 0.10) (Analysis 1.2) (Figure 4).

Figure 3. Forest plot of comparison: 1 Inhaled LAMAs versus placebo, outcome: 1.1 Change from baseline in FEV₁ (L) after 28 days of tiotropium 2.5µg.

Figure 4. Forest plot of comparison: 1 Inhaled LAMAs versus placebo, outcome: 1.2 Change from baseline in FEV₁ (L) after 28 days of Tiotropium 5µg.

GRADE: we found the quality of this evidence to be low.

2. Participant-reported outcomes (including QoL and symptom scores)

Two trials reported the change from baseline in CFQ-R domain scores, but no data were presented (Bradley 2014; Ratjen 2015). The authors state that there were no differences in CFQ-R domain scores after 12 weeks of treatment with tiotropium.

GRADE: low-quality evidence.

3. Adverse effects

a. frequency of adverse effects

Three trials provided data on the frequency of adverse events and more specifically drug-related adverse effects (Bradley 2014; Konstan 2015; Ratjen 2015). The Konstan trial measured adverse effects over 28 days, whilst the remaining two trials reported adverse effects over 12 weeks (Bradley 2014; Ratjen 2015).

i. medium term (7 to 28 days)

For all adverse events, Konstan found little difference between the tiotropium group and the placebo group at either the 2.5 µg dose level, RR 1.01 (95% CI 0.61 to 1.68) or at the 5.0 µg dose level, RR 0.97 (95% CI 0.59 to 1.60) (Analysis 1.3). Similarly for severe adverse events, little difference was found between tiotropium and placebo after 2.5 µg, RR 0.70 (95% CI 0.05 to 10.27) or 5 µg, RR 0.58 (95% CI 0.04 to 8.61) (Analysis 1.5). For trial-drug-related adverse events, the results showed a higher frequency of events in the tiotropium group, but the CIs are wide and the result was not significant; 2.5 µg, RR 2.14 (95% CI 0.09 to 49.08) and 5.0 µg, RR 1.75 (95% CI 0.20 to 15.25) (Analysis 1.7).

ii. longer term (28 days to three months)

Two trials reported adverse events over a three-month period (Bradley 2014; Ratjen 2015). Bradley reported the frequency of adverse events after 2.5 µg and 5 µg tiotropium to be similar across all treatment groups, RR 1.01 (95% CI 0.92 to 1.11), RR 0.98 (95% CI 0.90 to 1.06), respectively (Analysis 1.4) (Figure 5). The most commonly reported adverse events were cough, exacerbation of CF, pyrexia, nasopharyngitis and headache (Bradley 2014).

Figure 5. Forest plot of comparison: 1 Inhaled LAMAs versus placebo, outcome: 1.4 Any adverse event after 12 weeks of treatment.

The Ratjen trial only reported adverse events after inhalation of 5.0 µg tiotropium compared to placebo and found the frequency of adverse events to be similar between treatment and placebo groups (Ratjen 2015). When combined, the results of the Bradley trial and the Ratjen trial were not significantly different from placebo, RR 0.98 (95% CI 0.90 to 1.06) (Analysis 1.4) (Figure 5). The most commonly reported adverse event was cough (tiotropium 18% versus placebo 13%).

b. severity of adverse effects (where it has been reported)

i. medium term (7 to 28 days)

Konstan reported on severe adverse events and drug-related adverse events at both dose levels (Analysis 1.5; Analysis 1.7). When comparing tiotropium 2.5 µg to placebo, two participants (one from each group) experienced serious adverse events (both of which were exacerbation in CF); neither event was considered to be related to the trial drug and no symptoms associated with LAMAs were reported (Konstan 2015).

When trial-drug-related events were examined separately, the tiotropium group were more likely to experience adverse events than the placebo group at both doses; 2.5 µg, RR 2.14 (95% CI 0.09 to 49.08) and 5.0 µg, RR 1.75 (95% CI 0.20 to 15.25) but these results were not significant (Analysis 1.7).

ii. longer term (28 days to three months)

Both the Bradley and Ratjen trials reported on adverse events categorised into serious adverse events and trial-drug-related adverse events after 12 weeks of treatment (Bradley 2014; Ratjen 2015). There were no significant differences in either serious adverse events between the tiotropium 2.5 µg group or 5.0 µg compared to placebo, although there was a slightly higher risk in the tiotropium group; 2.5 µg, RR 1.88 (95% CI 0.77 to 4.59) and 5.0 µg, RR 1.43 (95% CI 0.72 to 2.84) (Analysis 1.6).

GRADE: we deemed the quality of the evidence relating to adverse events to be high.

Secondary outcomes**1. Number of exacerbations of respiratory symptoms**

Only one trial reported on the number of participants who experienced one or more exacerbations after 2.5 µg of tiotropium compared to placebo (Bradley 2014) and two trials reported this outcome after 5.0 µg of tiotropium (Bradley 2014; Ratjen 2015). There were fewer exacerbations both after tiotropium 2.5 µg, RR 0.82 (95% CI 0.41 to 1.65) and after 5.0 µg, RR 0.60 (95% CI 0.32 to 1.12), although neither result was significant (Analysis 1.9).

GRADE: we deemed the quality of this evidence to be moderate.

2. Need for hospitalisation or antibiotics or both

None of the trials reported on this outcome.

3. Time to first exacerbation

None of the trials reported on this outcome.

4. Other measures of lung function**a. PEFR (L per minute and % predicted)**

None of the trials reported on this outcome.

b. measures of bronchial hyper-responsiveness and bronchodilator responsiveness

None of the trials reported on this outcome.

c. FEF₂₅₋₇₅ (L per second and % predicted)

One trial measured FEF₂₅₋₇₅, but we were unable to enter the data into our analysis (Bradley 2014). Bradley reported that both doses of tiotropium led to adjusted mean improvements in FEF₂₅₋₇₅, but they were not significant (Bradley 2014). Ratjen found no significant difference between tiotropium and placebo for this outcome (Ratjen 2015).

d. FVC (L and % predicted)

None of the trials reported on this outcome.

e. any other measurements of lung function that are relevant**i. FEV₁ AUC_{0-4h} (% predicted and L)**

This outcome was a co-primary efficacy endpoint in two trials (Bradley 2014; Ratjen 2015). Only Bradley reported data for the lower dose of tiotropium (2.5 µg) which resulted in a significant improvement in FEV₁ AUC_{0-4h} after 12 weeks for both % predicted, MD 2.94% (95% CI 1.12 to 4.76) (Analysis 1.10) and L, MD 0.09 L (95% CI 0.03 to 0.15) (Analysis 1.11). Both Bradley and Ratjen reported on this outcome for the higher dose (5.0 µg) and when data were combined, improvements in FEV₁ AUC_{0-4h} were significantly in favour of tiotropium both in terms of % predicted, MD 2.59 (95% CI 1.28 to 3.89) (Analysis 1.10) and L, MD 0.09 L (95% CI 0.05 to 0.13) (Analysis 1.11) (Figure 6).

Figure 6. Forest plot of comparison: 1 Inhaled LAMAs versus placebo, outcome: 1.11 Change from baseline in adjusted FEV₁ AUC_{0-4h} after 12 weeks (L).

In both trials, a greater effect was seen in the 12 years and older age group at both dose levels than in the younger age group (Analysis

1.12; Analysis 1.13). At the lower dose level as reported only by Bradley, results for the younger group were not significant, MD

2.33% (95% CI -1.20 to 5.86), but they were for the older group, MD 3.12% (95% CI 1.03 to 5.21) ([Analysis 1.12](#)). At the higher dose level, combined data from Bradley and Ratjen again showed a non-significant result for the younger participants, MD 1.97% (95% CI -0.57 to 4.52) and a statistically significant result for the older age group, MD 2.83% (95% CI 1.37 to 4.30) ([Analysis 1.13](#)). Neither trial reported the effect in L separately for each age group.

GRADE: we found the quality of this evidence to be moderate.

ii. Trough FEV₁ (% predicted and L)

Results were similar for trough FEV₁, with Bradley showing a significant improvement in trough FEV₁ % predicted for all participants at the lower dose, MD 2.25% (95% CI 0.28 to 4.22) and combined data from Bradley and Ratjen also showing a significant difference between tiotropium 5.0 µg and placebo, MD 1.81% (95% CI 0.44 to 3.18) ([Analysis 1.14](#)). When the data were reported separately for the younger and older age groups, there was no significant improvement in either age group at the lower dose of tiotropium ([Analysis 1.15](#)). At the higher dose, however, the combined data from both trials ([Bradley 2014](#); [Ratjen 2015](#)) showed a significant improvement in trough FEV₁ (% predicted) in the older age group, MD 2.32 (95% CI 0.81 to 3.82) ([Analysis 1.16](#)). Results in L were only provided for all age groups combined. A significant improvement was shown in the tiotropium groups (both dose levels) compared to placebo; 2.5 µg, MD 0.06 L (95% CI 0.00 to 0.12) and 5.0 µg, MD 0.06 L (95% CI 0.03 to 0.10) ([Analysis 1.17](#)).

GRADE: we found the quality of this evidence to be moderate.

iii. FVC AUC_{0-4h} (% predicted and L)

This outcome was also reported by Bradley and Ratjen in the text of their trial reports, but no data were available for our analysis ([Bradley 2014](#); [Ratjen 2015](#)). Bradley showed an improvement in FVC AUC_{0-4h} (% predicted) after both doses of tiotropium, but only the higher dose reached significance (P = 0.002) ([Bradley 2014](#)). Ratjen reported no significant difference between tiotropium and placebo ([Ratjen 2015](#)).

iv. Trough FVC (% predicted and L)

Again, the Bradley and Ratjen trials reported this outcome, but did not provide data for our analysis ([Bradley 2014](#); [Ratjen 2015](#)). Bradley found improvements at both dose levels of tiotropium, but neither was statistically significant; 2.5 µg tiotropium (P = 0.4) and 5.0 µg tiotropium (P = 0.2) ([Bradley 2014](#)). Ratjen also reported no difference between 5.0 µg tiotropium and placebo for trough FVC (% predicted) (P = 0.19) ([Ratjen 2015](#)).

v. Residual volume (RV) and total lung capacity (TLC)

None of the trials reported on this outcome.

Beta-2 agonists versus muscarinic antagonists

None of the included trials compared beta-2 agonists with muscarinic antagonists.

DISCUSSION

Summary of main results

Our review aimed to look at the effect of long-acting bronchodilators on clinical outcomes including participant-reported outcomes and QoL. There have been very few trials looking at the effects of long-acting beta-2 agonist or muscarinic antagonist bronchodilators in people with CF and the trials that we found differed in design, duration of treatment and the outcomes measured. The trials included in this review only studied the effects of two drugs, one was the beta-2 agonist salmeterol and the other was the muscarinic antagonist bronchodilator tiotropium. A summary of the main results is also given in the summary of findings table for each comparison ([Summary of findings 1](#); [Summary of findings 2](#)).

Beta-2 agonists

The trial of salmeterol was published in 1998 and had a small number of participants (n = 16) ([Turchetta 1998](#)). The authors reported a significant improvement in FEV₁ after treatment with salmeterol, but did not present data on participant-reported outcomes, QoL or adverse events. In terms of secondary outcomes, the trial did not report on pulmonary exacerbations or hospitalisation, possibly due to the short duration of the treatment and follow-up. The results were published only as an abstract and the quality of the evidence was very low.

Muscarinic antagonists

The three trials that examined the effects of tiotropium at doses of 2.5 µg and 5.0 µg compared to placebo were much more recent and included larger numbers of participants (n = 1066) ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). Two of the trials had the same design and outcomes and formed phase II and III of the same clinical investigation ([Bradley 2014](#); [Ratjen 2015](#)); Konstan reported on the phase I trial related to these subsequent trials ([Konstan 2015](#)). The mean change in FEV₁ from baseline was only reported in one of the three trials, but no effect of tiotropium was seen at any dose ([Konstan 2015](#)).

Two trials measured QoL using the CFQ-R score and no difference was found between participants taking tiotropium and participants taking placebo after 12 weeks of treatment. There was also little difference between treatment and placebo groups for the frequency of adverse effects after either dose of tiotropium as measured by three of the trials ([Bradley 2014](#); [Konstan 2015](#); [Ratjen 2015](#)). Fewer participants reported one or more pulmonary exacerbations after 5.0 µg of tiotropium compared to placebo over 12 weeks, although this did not reach statistical significance ([Bradley 2014](#); [Ratjen 2015](#)).

The two linked trials measured FEV₁ AUC_{0-4h} and trough FEV₁ as their primary outcomes ([Bradley 2014](#); [Ratjen 2015](#)). The phase II trial (n = 510) which was judged to have an overall low risk of bias, found a significant improvement in FEV₁ AUC_{0-4h} after 12 weeks of tiotropium at both dose levels (2.5 µg and 5.0 µg) with a greater effect seen after the higher dose ([Bradley 2014](#)). The phase III trial, also judged to have an overall low risk of bias, looked only at the 5.0 µg dose and found there to be small but non-significant improvements in FEV₁ AUC_{0-4h} after 12 weeks of tiotropium ([Ratjen 2015](#)). When the two trials were entered into a meta-analysis,

the overall improvement in FEV₁ AUC_{0-4h} was significant ([Analysis 1.10](#)). Trough FEV₁ showed similar results, with the phase II paper reporting a significant improvement after tiotropium compared to placebo and the phase III trial showing no significant improvement. Both trials reported a greater effect in the 12 years or older age group ([Bradley 2014](#); [Ratjen 2015](#)).

Overall completeness and applicability of evidence

The single trial of a long-acting beta-2 agonist has only been published in abstract form to date and we have found no further data despite attempts to contact the authors ([Turchetta 1998](#)). The information is therefore limited and we were only able to present the results of the trial narratively.

The evidence for beta-2 agonists is older and only looks at the short- to medium-term effects of the drug ([Turchetta 1998](#)). Therefore we are unable to say how the treatment might improve lung function over the longer term. The trial also only recruited small numbers of participants and only children ([Turchetta 1998](#)). The fact that the trial did not report on our second primary outcome of participant-reported outcomes and QoL it makes it difficult for us to draw conclusions on how effective inhaled beta-2 agonist bronchodilators would be in improving QoL for people with CF.

The evidence for the muscarinic antagonist bronchodilator tiotropium was more robust and complete due to the larger numbers of participants and rigorous methodology employed in the trials of this drug. The three trials (full papers plus supplementary documentation) present results for both children and adults and report effects over a longer time period ranging from 28 days ([Konstan 2015](#)) to 12 weeks ([Bradley 2014](#); [Ratjen 2015](#)). This allowed us to look at whether treatment gradually improves symptoms over a longer time. Adverse effects were reported in all three trials which provides a more complete picture of whether there is a place for long-acting muscarinic antagonist bronchodilators for treating of children and adults with CF. There is a need to minimise adverse effects from treatments and the finding that there was little difference between long-acting bronchodilators and placebo is important.

However, two of the three trials of LAMAs did not report our primary outcome of change from baseline in FEV₁. Whilst they did report FEV₁, it was as FEV₁ area under the curve _{0-4h}. The trial authors selected this as their primary outcome as they felt it gave a more accurate measure of change in lung function over time ([Ratjen 2015](#)).

We should also note that two of the trials allowed included participants to continue their regular medication, which in some cases included a short-acting bronchodilator ([Bradley 2014](#); [Ratjen 2015](#)). Whilst the addition of a long-acting bronchodilator may improve lung function, if it is taken in addition to short-acting bronchodilators it will only add to the treatment burden rather than reduce it.

Quality of the evidence

Beta-2 agonists

The evidence presented has several limitations in terms of the number of trials and the quality of included trials. Only one trial was found which matched our inclusion criteria. The quality of the evidence from this trial is very limited as it is only reported in

abstract form and we have been unable to find further references to the trial ([Turchetta 1998](#)).

The trial reported on our primary outcome of change in FEV₁ from baseline but the quality of the evidence was downgraded twice due to risk of bias within the trial; once because of imprecision due to small numbers and once due to indirectness as the trial only included children ([Summary of findings 1](#)).

The trial did not report on our remaining primary or secondary outcomes.

Muscarinic antagonists

Although there are only a limited number of trials (n = 3) looking at the effects of LAMAs the overall quality of the evidence is moderate ([Summary of findings 2](#)).

However, only one of the three included trials of tiotropium reported on our primary outcome of change in FEV₁ from baseline. The quality of the evidence provided by this trial was deemed to be low and was downgraded once for risk of bias (due to unclear blinding methods) and once due to imprecision from a small sample size with only the one trial contributing data. Two trials measured QoL but the evidence was downgraded twice because analysable data were not presented in the paper (only narrative) and there was risk of bias from a lack of information. It is therefore difficult to draw conclusions for this outcome. The lack of such data is likely to be due to the relatively short-term nature of the trials which are not able to measure longer-term outcomes, but it illustrates an important gap in the evidence. The quality of evidence for our remaining primary outcome, adverse events, was deemed to be high. Two trials contributed to the adverse events data, both including large numbers of participants and there was no reason to downgrade the evidence.

In terms of the secondary outcome measures in our review, the quality of the evidence for participants reporting at least one pulmonary exacerbation during the trial period was deemed to be moderate. Similarly, for the other measures of lung function, the quality of evidence was moderate with the reason for downgrading being that this outcome is not routinely used in the clinical area.

Potential biases in the review process

It is unlikely that we have missed any trials; in addition to carrying out a rigorous search, we scanned references of included trials and contacted pharmaceutical companies for any unpublished work. Both authors scanned titles and extracted data independently to reduce bias and to detect errors in data extraction or interpretation.

Agreements and disagreements with other studies or reviews

Since the previously published version of the review ([Halfhide 2005](#)), there has been limited additional evidence published with respect to the use of long-acting bronchodilators. Similarly there have been few other reviews on the subject. Kent reviewed the "complex web" of CF and asthma and came to similar conclusions to this review; in particular, they emphasized the lack of long-term evidence ([Kent 2014](#)). However, since this review was completed, a further publication in PLoS One has reported on the impact of long-term tiotropium therapy on the annual decline in lung function ([Brandt 2016](#)). This retrospective cohort study estimated an annual

decline in lung function by utilizing longitudinal data for FEV₁, and demonstrated a significantly slower decline in the mean annual change in FEV₁ in people using tiotropium. Since this was not a RCT, it would not have been included in this Cochrane Review, but it does reinforce the need to perform further long-term studies of the use of long-acting bronchodilators in people with CF.

AUTHORS' CONCLUSIONS

Implications for practice

Since the publication of the previous Cochrane Review on bronchodilators for people with cystic fibrosis (CF) there has been no significant advance in the literature for evidence for long-acting beta-2 agonists. The evidence presented here is very low quality and does not add to our understanding of the effects on our specified outcomes.

The trials of long-acting muscarinic antagonists presented here are more robust than those of long-acting beta-2 agonists. The trials of muscarinic antagonists demonstrated no significant between tiotropium compared to placebo in our primary outcome of change from baseline in forced expiratory volume in one second (FEV₁) (L), although there was a significant increase in an alternative measure of FEV₁ (FEV₁ area under the curve (AUC)_{0-4h}). This measure was chosen by the trial authors as it gives a better measure of the effect over time. However, it is not a measure that is currently used in clinical practice (NICE 2017).

We found moderate-quality evidence that there was no significant effect on quality of life as measured by Cystic Fibrosis Quality of Life - Revised (CFQ-R) and higher-quality evidence that there were no significant differences in adverse events between tiotropium and placebo.

Given the burden of treatment that people with CF already have, clinical benefit of a long-acting bronchodilator should be proven to justify its continuing use. This could be clinically through reduction in symptoms or improvement in spirometry through reversibility testing. Without evidence of a clinical benefit, current practice regarding the use of long-acting muscarinic antagonists in people with CF should not change. In line with our conclusions on the use of long-acting beta-2 agonists, individuals may benefit from using muscarinic antagonists, but there is not enough evidence to support their use in the whole CF population.

Implications for research

There is limited evidence that either long-acting beta-2 agonist or muscarinic antagonist bronchodilators are effective in improving

measures of lung function and this is mainly in the short term. Four trials were excluded due to the cross-over design being inappropriate for looking at the effects of long-acting medication. If we want to assess the long-term effects of long-acting bronchodilators, larger trials of a more robust design (to reduce bias) are required. Parallel trials are much more appropriate for determining the effects of bronchodilators in a population where lung function is unstable and is generally progressive.

The objectives of our review were primarily to look at the effect of long-acting bronchodilators on FEV₁, participant-reported outcomes (e.g. quality of life) and adverse events. All the trials looked at the effect of treatment on measures of lung function, although the more rigorous trials looked only at FEV₁ AUC_{0-4h} rather than change in FEV₁ from baseline (either as % predicted or in L). Future trials could improve the evidence base if there was a consistent use of the same outcome measures (particularly measures which are meaningful in the clinical area) over the same time-scales.

Only two trials assessed quality of life using CFQ-R scores. These were also the only trials to report on pulmonary exacerbations; no trials looked at hospitalisation. This is likely to be due to the fact that they were medium-term trials and not of sufficient duration to measure these outcomes. It is important that any future trials measure outcomes which are used in the clinical area and are meaningful to both clinicians and patients. Trials need to be of a sufficient duration to study the effects on outcomes which may be of equal importance to people with CF, such as improvements in quality of life and respiratory symptoms.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bradley 2014

Study characteristics

Methods	<p>RCT.</p> <p>Placebo-controlled.</p> <p>Parallel design.</p> <p>Duration: 12 weeks.</p> <p>Location: multicentre, multinational.</p>
Participants	<p>Participants had to be able to perform spirometric manoeuvres according to ATS standards and to be clinically stable (no evidence of acute respiratory tract infection or pulmonary exacerbation requiring use of antibiotics or oral corticosteroids within four weeks of screening). FEV₁ % predicted within 10% of assessment studies, 2 CF genes.</p>

Bradley 2014 (Continued)

Number of participants entering trial n = 510: tiotropium 2.5.0 µg n = 166; tiotropium 5.0 µg n = 176; placebo n = 168.

Age: all ages were included except in Russia where children under 6 years were excluded.

Total cohort: mean (SD) age: 20.9 (11.6) years; range 5 to 69 years. Stratified as: ≤ 11 years n = 138 (27.1%); ≥ 12 years n = 372 (72.9%).

Tiotropium 2.5.0 µg: mean (SD) age: 21.5 (12.0) years.

Tiotropium 5.0 µg: mean (SD) age: 20.7 (11.3) years.

Gender: 53.9% male; 46.1% female.

Disease severity:

Total cohort: mean (SD) % predicted FEV₁ 76.0% (24.3).

Tiotropium 2.5.0 µg: mean (SD) % predicted FEV₁ 75.4% (26.7).

Tiotropium 5.0 µg: mean (SD) % predicted FEV₁ 75.9% (22.6).

Placebo: mean (SD) % predicted FEV₁ 76.6% (23.8).

Interventions	<p>Intervention 1: tiotropium bromide delivered by Respimat Soft Mist Inhaler 2.5.0 µg (2 inhalations of 1.25.0 µg once daily).</p> <p>Intervention 2: tiotropium bromide delivered by Respimat Soft Mist Inhaler 5.0 µg (2 inhalations of 2.5.0 µg once daily).</p> <p>Intervention 3: placebo solution for inhalation (2 inhalations once daily).</p>
Outcomes	<p>Primary outcome: change from baseline in FEV₁ AUC_{0-4h} (% predicted and L), trough FEV₁ (% predicted and L).</p> <p>Secondary outcomes: FVC AUC, static lung hyperinflation (RV/TLC), number of participants reporting ≥ 1 pulmonary exacerbation, CFQ-R scores, adverse events (all, serious AE, trial-drug-related AE, other significant AE, AE leading to discontinuation of trial drug).</p> <p>Co-primary endpoints were measured at baseline and end of weeks 4, 8 and 12 (end of treatment). There was a follow-up visit 30 days post treatment or at point of discontinuation from the trial. PFTs were performed pre-dose (10 minutes prior to trial drug inhalation) and at 1, 2, 3 and 4 hours after inhalation; at weeks 4 and 8, PFTs were measured 30 minutes prior to inhalation. RSSQ was measured at 0, 2, 4 and 12 weeks. RV/TLC at baseline and week 12 (15 minutes prior to trial drug inhalation and 3 hours 45 minutes after inhalation). CFQ-R – weeks 1 and 12.</p>
Notes	<p>All participants continued to receive their standard of care treatment during the trial. They were allowed to continue using SABA and LABA if they were stabilised at least 4 weeks prior to randomisation. There was a 6-hour and 12-hour washout period for SABA and LABA prior to spirometric measurements.</p> <p>Concomitant medications: 74% of total were taking concomitant medications; SABA 304 (59.6%); LABA 188 (36.9).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Boehringer Ingelheim generated a randomisation schedule using simple blocked randomisation with a block size of 6.</p> <p>Participants were allocated in a 1:1:1 ratio.</p>

Bradley 2014 (Continued)

Allocation concealment (selection bias)	Low risk	Medication was prepared and coded by Boehringer Ingelheim in a blinded fashion and they provided all supplies.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial. Laboratory staff were given the allocation code but kept it confidential.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An emergency code break was available to the investigator. Prior to unblinding of the trial database, the random code was forwarded to the bio-analytical laboratory to conduct the analytical determinations. The responsible person confirmed in writing that the random plan was treated confidentially and that all unblinding information was restricted to the laboratory staff.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% lost to follow-up, reasons given. 21 discontinued trial: 3 consent withdrawn; 14 AE; 1 lost to follow-up, 3 other.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the trial methodology were reported in the results.
Other bias	Unclear risk	Funding was provided by Boehringer Ingelheim who were also involved in trial design, collection and analysis, interpretation of data, preparation of the manuscript and decision to publish. Conflicts of interest: 2 authors acted as consultants for Boehringer Ingelheim and were Principal Investigators for the phase 2 and 3 trials. 3 authors are employees of Boehringer Ingelheim.

Konstan 2015
Study characteristics

Methods	<p>RCT.</p> <p>Placebo-controlled.</p> <p>Parallel design.</p> <p>Stepwise dose-escalation trial.</p> <p>Duration: single dose part of trial followed by 28 days treatment. If participants participated in both arms (with same dose) there was a 30-day washout between arms</p> <p>Location: multicentre, 12 sites in the USA.</p>
Participants	<p>92 participants were randomised to receive the trial drug. Single-dose trial only n = 30, multiple-dose trial only n = 41, both single-dose and multiple-dose trials n = 17.</p> <p><i>Single-dose trial</i></p> <p>Participants</p> <p>Whole cohort (n = 51): tiotropium n = 38, placebo n = 13.</p> <p>Aged 5 - ≤ 11 years (n = 25): tiotropium n = 19, placebo n = 6.</p> <p>Aged ≥ 12 years (n = 26): tiotropium n = 19, placebo n = 7.</p>

Konstan 2015 (Continued)

Age (mean (SD))

Participants aged ≤ 11: tiotropium 9.6 (1.4) years, placebo 9.5 (0.5) years.

Participants aged ≥ 12: tiotropium 22.5 (6.8) years, placebo 27.3 (10.4) years.

Gender

Whole cohort: 26 (51%) male.

Participants aged ≤ 11: 14 (56%) male.

Participants aged ≥ 12: 12 (46%) male.

Disease severity (FEV₁ % predicted mean (SD))

Participants aged ≤ 11; tiotropium 98.7 (12.8)%, placebo 97.1 (13.9)%.

Participants aged ≥ 12: tiotropium 73.1 (23.4)%, placebo 70.8 (28.0)%.

Multiple-dose trial

Participants

Whole cohort (n = 58): tiotropium n = 44, placebo n = 14.

Aged 5 - ≤ 11 years (n = 24): tiotropium n = 19, placebo n = 5.

Aged ≥ 12 years (n = 34); tiotropium n = 25, placebo n = 9.

Age (mean (SD))

Participants aged ≤ 11: tiotropium 8.9 (1.7) years, placebo 8.4 (1.3) years.

Participants aged ≥ 12: tiotropium 30.2 (12.7) years, placebo 28.7 (14.5) years.

Gender

Whole cohort: 32 (55.5%) male.

Participants aged ≤ 11: 14 (58%) male.

Participants aged ≥ 12: 18 (53%) male.

Disease severity (FEV₁ % predicted mean (SD))

Participants aged ≤ 11: tiotropium 97.5 (15.1)%, placebo 91.2 (12.4)%.

Participants aged ≥ 12: tiotropium 74.4 (21.4)%, placebo 68.8 (23.3)%.

Interventions	<p><i>Single-dose trial</i></p> <p>Intervention 1: 1 dose of tiotropium bromide 2.5 µg, 5.0 µg or 10.0 µg via the Respimat® SMI as an add-on to standard therapy.</p> <p>Intervention 2: placebo via the Respimat® SMI as an add-on to standard therapy.</p> <p><i>Multiple-dose trial</i></p> <p>Intervention 1: tiotropium bromide 2.5 µg, 5.0 µg or 10.0 µg via the Respimat® SMI, 1x daily for 28 days as an add-on to standard therapy.</p> <p>Intervention 2: placebo via the Respimat® SMI, 1x daily for 28 days as an add-on to standard therapy.</p>
Outcomes	<p>Spirometry (change from baseline in FEV₁ (L)), AEs (any AE, severe AEs, significant AEs and investigator-defined drug-related AEs (using the Medical Dictionary for Regulatory Activities, version 11)).</p>

Konstan 2015 (Continued)

Single-dose trial

Measured at baseline, 30 minutes post dose

Multiple-dose trial

Measured at baseline, 30 minutes post dose on Day 1, 30 minutes pre dose on Day 28, 30 minutes post dose on Day 28.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment assignment was made by means of a third-party IXRS. Participants were allowed to choose which trial (single-dose or multiple-dose) they entered but were then randomised.
Allocation concealment (selection bias)	Low risk	Allocation was made by a third-party IXRS.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind but methods not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear which parties were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/92 (3.3%) were excluded with reasons given. 1 participant in the younger group discontinued due to a non-serious AE of increased cough (tiotropium 5.0 µg group). 2 participants in the older group discontinued due to a serious AE of pulmonary exacerbation (placebo group) and a non-serious AE of increased mucus thickness (tiotropium 2.5 µg group).
Selective reporting (reporting bias)	Low risk	Protocol was not available but all outcomes listed in the methods section were reported in the results.
Other bias	Unclear risk	Sponsored by Boehringer Ingelheim Pharmaceuticals. 4 authors were employees of Boehringer Ingelheim Pharmaceuticals and one acted as a consultant.

Ratjen 2015

Study characteristics

Methods	RCT.
	Placebo-controlled.
	Parallel design.
	Duration: 12 weeks.

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Ratjen 2015 (Continued)

	Location: Multicentre trial, 99 sites in 20 countries.	
Participants	<p>464 participants randomised: tiotropium n = 309, placebo n = 155.</p> <p>Number receiving intended treatment: tiotropium n = 308/309, placebo n = 155/155.</p> <p>Age (mean (SD))</p> <p>Whole cohort: 19.8 (12.5) years, range 5 months (0.4 years) to 70.5 years.</p> <p>Tiotropium group: 19.3 (12.0) years.</p> <p>Placebo group: 20.6 (13.6) years.</p> <p>Gender</p> <p>Tiotropium group: 169 (54.9%) males.</p> <p>Placebo group: 90 (58.1%) males.</p> <p>Disease severity (mean (SD) FEV₁ % predicted)</p> <p>Whole cohort: tiotropium group 76.1 (22.5)%, placebo group 77.5 (24.4)%.</p> <p>Participants ≤ 11 years: tiotropium group 89.8 (17.8)%, placebo group 90.6 (19.6)%.</p> <p>Participants ≥ 12 years: tiotropium group 69.4 (21.5)%, placebo group 71.3 (24.0)%.</p>	
Interventions	<p>Intervention 1: 5.0 µg tiotropium (2 puffs twice daily) via the Respimat®.</p> <p>Intervention 2: placebo (2 puffs twice daily) via the Respimat® (with VHC for participants aged < 5 years).</p>	
Outcomes	<p>FEV₁ AUC_{0-4h} (% predicted and L), trough FEV₁ (% predicted and L), FVC AUC_{0-4h}, trough FVC, trough FEF₂₅₋₇₅ (% predicted), number of participants reporting ≥ 1 pulmonary exacerbation (RSSQ method), change from baseline in CFQ-R scores, AEs (all, serious AE, trial-drug-related AE, other significant AE, AE leading to discontinuation of trial drug).</p> <p>PFTs measured at screening visit (1 week before start of treatment and at weeks 1, 4 and 12), performed pre dose (10 minutes prior to drug inhalation) at 30 minutes and at 1, 2, 3 and 4 hours after inhalation. At week 4 PFTs were only carried out 30 minutes prior to drug administration. A single PFT was performed at the end of treatment.</p>	
Notes	<p>Baseline concomitant medications (n,%)</p> <p>Inhaled antibiotics: tiotropium 113/308 (36.7%), placebo 74/155 (47.7%).</p> <p>Short-acting bronchodilators: tiotropium 150/308 (48.7%), placebo 80/155 (51.6%).</p> <p>Inhaled corticosteroids: tiotropium 138/308 (44.8%), placebo 67/155 (43.2%).</p> <p>Long-acting bronchodilators: tiotropium 115/308 (37.3%), placebo 57/155 (36.8%).</p> <p>An open-label extension assessing long-term safety was also carried out from 12 to 60 weeks.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Boehringer Ingelheim produced the computer-generated random sequence with a block size of 3 using an IXRS; participants allocated in a 1:2 (placebo:active) ratio in a blinded fashion

Ratjen 2015 (Continued)

Randomisation was performed at week 1 (day 1), and was stratified by age group (< 5 years, 5 to 8 years, 9 to 11 years and ≥ 12 years).		
Allocation concealment (selection bias)	Low risk	Boehringer Ingelheim generated the sequence using an IXRS, prepared and coded the medication in a blinded fashion and provided all trial supplies. There was an emergency code break but this could only be opened in emergency situations when the identity of the trial drug had to be known to the investigator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The medication was prepared and coded in a blinded fashion. Double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinding was restricted to laboratory staff.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Tiotropium: 14/309 (4.5%) discontinued trial with reasons given (AE n = 6, lost to follow-up n = 2, consent withdrawn n = 2, other n = 4). Placebo 8/155 (5.2%) discontinued trial with reasons given (AE n = 2, non-compliance with protocol n = 2, lost to follow-up n = 1, consent withdrawn n = 1, other n = 2).
Selective reporting (reporting bias)	Low risk	All outcomes given in methods section are reported in the results. Extra information is available in supplementary documentation.
Other bias	Unclear risk	Funding was provided by Boehringer Ingelheim, who were also involved in trial design, collection, analysis and interpretation of data, writing the report and decision to publish. FR (first author) acts as a consultant for Boehringer Ingelheim and is principal investigator. Another author acts as a consultant for Boehringer Ingelheim. 5 other authors are employees of Boehringer Ingelheim.

Turchetta 1998

Study characteristics

Methods	RCT. Parallel design. Duration: 1 month. Location: Not stated
Participants	16 children with CF. Salmeterol group n = 7, no treatment group n = 9. Age (mean (SD)): 13.9 (3.1) years. Gender: 11 males (68.7%) and 5 females (31.3%). Disease severity: mean (SD) FEV ₁ 72 (19) % predicted.
Interventions	Intervention 1: 2 puffs salmeterol by spacer twice daily.

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Turchetta 1998 (Continued)

Intervention 2: no salmeterol treatment.

Outcomes	FEV ₁ (no unit of measurement given), FVC (no unit of measurement given), VO _{2 max} obtained via stress test on the treadmill (Bruce protocol).
Notes	Concomitant medications: dietary supplementation, pancreatic enzymes, physiotherapy, mucolytics and aerosol antibiotics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described (abstract only).
Allocation concealment (selection bias)	Unclear risk	Not described (abstract only).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The comparator was no treatment rather than a placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described (abstract only). The comparator was no treatment rather than a placebo, but no information as to whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes listed in the methods were reported in the results. The authors stated that FVC was measured but no results were reported.
Other bias	Unclear risk	Abstract only. Not enough information to be able to make a judgement.

AE: adverse event

CF: cystic fibrosis

FEF₂₅₋₇₅: mid-peak expiratory flow

FEV₁: forced expiratory volume in one second

FEV₁ AUC_{0-4h}: forced expiratory volume in one second area under the curve 0-4 hours

FVC: forced expiratory volume

IC: inspiratory capacity

IXRS: interactive voice and web-response system

LABA: long-acting beta-agonist

MDI: metered dose inhaler

PFT: pulmonary function test

RCT: randomised controlled trial

RSSQ: Respiratory and Systemic Symptoms Questionnaire

RV: residual volume

SABA: short-acting beta-agonist

SD: standard deviation

S_{tc}O: transcutaneous arterial oxyhaemoglobin saturation

TLC: total lung capacity

VO_{2 max}: maximal oxygen consumption

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dodd 2005	Intervention not appropriate. The trial looks at the effect of a short-acting bronchodilator.
Hordvik 1999	This is a 3-arm cross-over trial run over 3 days. There is no washout period in between treatment days.
Hordvik 2002	The comparator is a short-acting bronchodilator and not a placebo or no treatment or another long-acting bronchodilator.
Keir 2007	Cross-over trial.
Konstan 2014	Intervention not appropriate i.e. not a long-acting inhaled bronchodilator. Looked at the effect of BIIL 284 BS, a LTB4 receptor antagonist which was taken orally rather than inhaled.
Nielsen 2006	Inappropriate trial design - review.
Nikolaizik 1996a	Intervention not appropriate, i.e. not a long-acting inhaled bronchodilator. Looked at the effect of inhaled tobramycin.
Orlik 2002	Intervention not appropriate. The trial looks at the effect of a short-acting bronchodilator.
Regelmann 1990	Intervention not appropriate i.e. not a long-acting bronchodilator. Looked at the effect of parenteral antibiotics versus placebo.
Rodrigues 2008	Cross-over trial.
Salvatore 2002	Cross-over trial.
Serisier 2007	Intervention not appropriate. The trial looks at the effect of a short-acting bronchodilator.
Turchetta 1996	The comparator is a short-acting bronchodilator and not a placebo, no treatment or another long-acting bronchodilator.
Weintraub 1989	Intervention not appropriate, i.e. not a long-acting bronchodilator. Examined the effects of the short-acting muscarinic antagonist bronchodilator ipratropium bromide.
Wiebicke 1990	Intervention not appropriate, i.e. not a long-acting bronchodilator. Examined the effects of the short-acting muscarinic antagonist bronchodilator ipratropium bromide.
Ziebach 2001	Not looking at a long-acting bronchodilator. Looks at the effects of salbutamol and a combination of ipratropium and salbutamol.

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Inhaled LAMAs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change from baseline in FEV₁ (L) after 28 days of tiotropium 2.5µg	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.13, 0.09]
1.1.1 Participants aged 5 - ≤ 11 years	1	13	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.20, 0.10]
1.1.2 Participants aged ≥ 12 years	1	21	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.15, 0.17]
1.2 Change from baseline in FEV₁ (L) after 28 days of Tiotropium 5µg	1	38	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.10, 0.10]
1.2.1 Participants aged 5 - ≤ 11 years	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.16, 0.14]
1.2.2 Participants aged ≥ 12 years	1	22	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.14, 0.16]
1.3 Any adverse event after 28 days of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 Tiotropium 2.5 µg	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.61, 1.68]
1.3.2 Tiotropium 5.0 µg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.60]
1.4 Any adverse event after 12 weeks of treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 Tiotropium 2.5 µg	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.11]
1.4.2 Tiotropium 5.0 µg	2	807	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.06]
1.5 Severe adverse events after 28 days of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 Tiotropium 2.5 µg	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.05, 10.27]
1.5.2 Tiotropium 5.0 µg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.04, 8.61]
1.6 Severe adverse events after 12 weeks of treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 Tiotropium 2.5 µg	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.77, 4.59]
1.6.2 Tiotropium 5.0 µg	2	807	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.72, 2.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Trial drug-related adverse events after 28 days of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Tiotropium 2.5 µg	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.09, 49.08]
1.7.2 Tiotropium 5.0 µg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.20, 15.25]
1.8 Trial drug-related adverse events after 12 weeks of treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 Tiotropium 2.5 µg	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.54, 2.17]
1.8.2 Tiotropium 5.0 µg	2	807	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.77, 1.98]
1.9 Participants reporting ≥ 1 pulmonary exacerbation during 12 weeks of treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 Tiotropium 2.5 µg	1	333	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.41, 1.65]
1.9.2 Tiotropium 5.0 µg	2	805	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.32, 1.12]
1.10 Change from baseline in adjusted FEV ₁ AUC _{0-4h} after 12 weeks of treatment (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.10.1 Tiotropium 2.5 µg	1	321	Mean Difference (IV, Fixed, 95% CI)	2.94 [1.12, 4.76]
1.10.2 Tiotropium 5.0 µg	2	770	Mean Difference (IV, Fixed, 95% CI)	2.59 [1.28, 3.89]
1.11 Change from baseline in adjusted FEV ₁ AUC _{0-4h} after 12 weeks (L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 Tiotropium 2.5 µg	1	321	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.03, 0.15]
1.11.2 Tiotropium 5.0 µg	2	770	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.05, 0.13]
1.12 Change from baseline in adjusted FEV ₁ AUC _{0-4h} (% predicted) after 12 weeks of tiotropium 2.5 µg by age group	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 Age group 5 to ≤11 years	1	85	Mean Difference (IV, Fixed, 95% CI)	2.33 [-1.20, 5.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.2 Age group ≥ 12 years	1	236	Mean Difference (IV, Fixed, 95% CI)	3.12 [1.03, 5.21]
1.13 Change from baseline in adjusted FEV ₁ AUC _{0-4h} (% predicted) after 12 weeks of tiotropium 5.0 μ g by age group	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.13.1 Age group 5 to ≤ 11 years	2		Mean Difference (IV, Fixed, 95% CI)	1.97 [-0.57, 4.52]
1.13.2 Age group ≥ 12 years	2		Mean Difference (IV, Fixed, 95% CI)	2.83 [1.37, 4.30]
1.14 Change from baseline in adjusted trough FEV ₁ (% predicted) after 12 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.14.1 Tiotropium 2.5 μ g	1	321	Mean Difference (IV, Fixed, 95% CI)	2.25 [0.28, 4.22]
1.14.2 Tiotropium 5.0 μ g	2	772	Mean Difference (IV, Fixed, 95% CI)	1.81 [0.44, 3.18]
1.15 Change from baseline in adjusted trough FEV ₁ (% predicted) after 12 weeks of treatment with 2.5 μ g tiotropium by age	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.15.1 Age group 5 to ≤ 11 years	1		Mean Difference (IV, Fixed, 95% CI)	3.54 [-0.24, 7.32]
1.15.2 Age group ≥ 12 years	1		Mean Difference (IV, Fixed, 95% CI)	1.76 [-0.47, 3.99]
1.16 Change from baseline in adjusted trough FEV ₁ (% predicted) after 12 weeks of treatment with tiotropium 5.0 μ g	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.16.1 Age group 5 - ≤ 11 years	2		Mean Difference (IV, Fixed, 95% CI)	0.88 [-1.76, 3.53]
1.16.2 Age group ≥ 12 years	2		Mean Difference (IV, Fixed, 95% CI)	2.32 [0.81, 3.82]
1.17 Change from baseline in adjusted trough FEV ₁ after 12 weeks (L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.17.1 Tiotropium 2.5 μ g	1	321	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.00, 0.12]
1.17.2 Tiotropium 5.0 μ g	2	763	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.03, 0.10]

Analysis 1.1. Comparison 1: Inhaled LAMAs versus placebo, Outcome 1: Change from baseline in FEV₁ (L) after 28 days of tiotropium 2.5µg

Analysis 1.2. Comparison 1: Inhaled LAMAs versus placebo, Outcome 2: Change from baseline in FEV₁ (L) after 28 days of Tiotropium 5µg

**Analysis 1.3. Comparison 1: Inhaled LAMAs versus placebo,
Outcome 3: Any adverse event after 28 days of treatment**

**Analysis 1.4. Comparison 1: Inhaled LAMAs versus placebo,
Outcome 4: Any adverse event after 12 weeks of treatment**

**Analysis 1.5. Comparison 1: Inhaled LAMAs versus placebo,
Outcome 5: Severe adverse events after 28 days of treatment**

**Analysis 1.6. Comparison 1: Inhaled LAMAs versus placebo,
Outcome 6: Severe adverse events after 12 weeks of treatment**

Analysis 1.7. Comparison 1: Inhaled LAMAs versus placebo, Outcome 7: Trial drug-related adverse events after 28 days of treatment

Analysis 1.8. Comparison 1: Inhaled LAMAs versus placebo, Outcome 8: Trial drug-related adverse events after 12 weeks of treatment

Analysis 1.9. Comparison 1: Inhaled LAMAs versus placebo, Outcome 9: Participants reporting ≥ 1 pulmonary exacerbation during 12 weeks of treatment

Analysis 1.10. Comparison 1: Inhaled LAMAs versus placebo, Outcome 10: Change from baseline in adjusted FEV₁ AUC_{0-4h} after 12 weeks of treatment (% predicted)

Analysis 1.11. Comparison 1: Inhaled LAMAs versus placebo, Outcome 11: Change from baseline in adjusted FEV₁ AUC_{0-4h} after 12 weeks (L)

Analysis 1.12. Comparison 1: Inhaled LAMAs versus placebo, Outcome 12: Change from baseline in adjusted FEV₁ AUC_{0-4h} (% predicted) after 12 weeks of tiotropium 2.5 µg by age group

Analysis 1.13. Comparison 1: Inhaled LAMAs versus placebo, Outcome 13: Change from baseline in adjusted FEV₁ AUC_{0-4h} (% predicted) after 12 weeks of tiotropium 5.0 µg by age group

Analysis 1.14. Comparison 1: Inhaled LAMAs versus placebo, Outcome 14: Change from baseline in adjusted trough FEV₁ (% predicted) after 12 weeks

Analysis 1.15. Comparison 1: Inhaled LAMAs versus placebo, Outcome 15: Change from baseline in adjusted trough FEV₁ (% predicted) after 12 weeks of treatment with 2.5 µg tiotropium by age

Analysis 1.16. Comparison 1: Inhaled LAMAs versus placebo, Outcome 16: Change from baseline in adjusted trough FEV₁ (% predicted) after 12 weeks of treatment with tiotropium 5.0 µg

Analysis 1.17. Comparison 1: Inhaled LAMAs versus placebo, Outcome 17: Change from baseline in adjusted trough FEV₁ after 12 weeks (L)

ADDITIONAL TABLES

Table 1. Characteristics of excluded cross-over trials

Trial	Trial characteristics	Participants	Interventions	Summary of results
Hordvik 1999	<p>Duration: 3 days (salmeterol vs placebo given on one day of the 3 day trial).</p> <p>Design: cross-over RCT.</p> <p>Location: single-centre trial, USA.</p>	<p>Number: 18.</p> <p>Age: mean (range) age 24 (14 – 36) years.</p> <p>Gender: 38.9 % male.</p> <p>Disease status: mean % predicted FEV₁ 56% (95% CI 22% to 91%).</p>	<p>Intervention 1: salmeterol via MDI (42 mcg) single dose given on one day versus placebo.</p> <p>Comparator: placebo via MDI, no details given.</p>	<p>FEV₁: mean % change in FEV₁ from baseline to 24 hours was 7.3% compared to 1.5% for placebo P < 0.04.</p> <p>There was significant carry over to the next morning for salmeterol compared to placebo.</p>
Keir 2007	<p>Duration: 24 hours (1 day).</p> <p>Design: cross-over RCT.</p> <p>Location: single-centre, Australia.</p>	<p>Number: 11.</p> <p>Age: mean (SD) age 26.5 (5.4) years.</p> <p>Gender: 45.5 % males.</p> <p>Disease status: mean (SD) FEV₁ % predicted 45.4 (8.98).</p>	<p>Intervention 1: tiotropium (no details of dose).</p> <p>Comparator: placebo (no details given).</p>	<p>FEV₁: Keir was unable to show an effect from a single dose of tiotropium after 24 hours and there was no significant difference between tiotropium and placebo at any of the time points measured.</p> <p>No other outcomes reported.</p>

Table 1. Characteristics of excluded cross-over trials (Continued)

Rodrigues 2008	Duration: 24 hours. Design: cross-over RCT. Location: not stated.	Number: 20. Age: range 6 to 20 years. Gender: not stated. Disease status: FEV ₁ > 40% predicted.	Intervention 1: single dose of inhaled tiotropium (18.0 µg). Comparator: single dose of placebo (empty capsule).	FEV₁: no significant change in FEV ₁ after treatment with a single dose of tiotropium compared with placebo. Other lung function measures: significant increase in airway conductance and a significant decrease in bronchial resistance after a single dose of tiotropium P < 0.0001. FVC: no significant change in FVC after the inhalation of tiotropium or placebo. No other outcomes reported.
Salvatore 2002	Duration: 4 days. Design: cross-over RCT. Location: single-centre trial, Italy.	Number: 23. Age: range 18.5 to 36.6 years. Gender: 56.5 % male. Disease status: mean (SD) FVC % predicted 63.2 (10)%, mean (SD) FEV ₁ % predicted 49.8 (12.9)%.	Intervention 1: 4 puffs of salmeterol xinofoate 84.0 µg via MDI. Comparator: placebo via MDI (no details given).	FEV₁: Salvatore reported significant improvements in FEV ₁ % predicted (increase of 10.6% P < 0.0001) the morning after treatment with salmeterol in the group of participants who responded to albuterol on the first day of the four-day trial. Those participants who did not respond to albuterol showed no significant improvement in FEV ₁ % predicted after treatment with salmeterol. Other lung function measures: FEF ₂₅₋₇₅ There was a significant improvement of 25.4%, P < 0.0001 in mean FEF ₂₅₋₇₅ the morning after treatment with salmeterol was seen in responders to an albuterol challenge. No other outcomes reported.

CF: cystic fibrosis

FEF₂₅₋₇₅: mid-peak expiratory flow

FEV₁: forced expiratory volume in one second

FVC: forced expiratory volume

MDI: metered dose inhaler

RCT: randomised controlled trial

SD: standard deviation

APPENDICES

Appendix 1. Glossary

Term	Explanation
acetylcholine	a neurotransmitter in the autonomic nervous system
adrenoceptor	G protein coupled receptors that are targets for the catecholamines, especially adrenaline and noradrenaline
airway hyper-responsiveness	an exaggerated response of the airway to no specific stimuli which results in airway obstruction

(Continued)

atopic asthma	asthma that begins before six year of age and is associated with atopy (the genetic tendency to develop allergic diseases and typically associated with heightened immune responses to common allergens)
bronchi	the main passages of airway in the respiratory tract that conduct air to the lungs
bronchiectasis	abnormal widening of the bronchi or their branches
bronchodilators	drugs that cause widening of the bronchi and bronchioles, decreasing resistance in the airway and increasing air flow to the lungs
hypercarbia	an abnormally high level of carbon-dioxide in the blood
hypoxaemia	an abnormally low concentration of oxygen in the blood
intracellular	inside the cell
lipophilic tail	having an affinity for lipids
mucociliary clearance	the movement of mucus covering the respiratory tract lining by the beating of the cilia
mucosal oedema	the build up of fluid within the mucosal layer of tissue in the lungs
muscarinic receptors	proteins which contain a recognition site for acetylcholine; they stimulate smooth muscle contractions
myosin	a protein that converts chemical energy in the form of adenosine triphosphate (ATP) to mechanical energy.
phosphorylation	a mechanism of regulating protein function and turns many protein enzymes on and off
viscid secretions	secretions which are thick and sticky

Appendix 2. Embase search strategy

1. Clinical Trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.tw.
13. (allocated adj2 random).tw.

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14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. Placebo\$.tw.
18. Prospective study/
19. or/1-18
20. Case study/
21. Case report.tw.
22. Abstract report/ or letter/
23. or/20-22
24. 19 not 23
25. exp cystic fibrosis/
26. cystic fibrosis.tw.
27. (fibrocystic adj disease).tw.
28. (fibrocystic adj pancreas).tw.
29. mucoviscido\$.tw.
30. (cystic\$ adj10 fibros\$).tw.
31. or/25-30
32. 24 and 31
33. limit 32 to human
34. bronchodilator\$.tw.
35. inhaled.tw.
36. 34 and 35
37. 24 and 33 and 36

WHAT'S NEW

Date	Event	Description
26 May 2021	Review declared as stable	Due to a lack of research in this area, it has been agreed that this review will no longer be updated.

HISTORY

Protocol first published: Issue 2, 2016

Review first published: Issue 12, 2017

CONTRIBUTIONS OF AUTHORS

Protocol 2016

Sherie Smith is the lead author of the revised protocol looking solely at long-acting inhaled bronchodilators, with clinical input and advice from Dr Christopher Edwards.

Review 2017

Sherie Smith and Dr Edwards were responsible for filtering search results and applying inclusion criteria to identify eligible trials, data extraction, risk of bias assessment, data analysis and interpretation of results, and drafting the final review.

DECLARATIONS OF INTEREST

Sherie Smith declares no known potential conflict of interest.

Dr Christopher Edwards declares no known potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a post hoc change we excluded cross-over trials due to the carry-over effects of long-acting medication since it would not be possible to ensure that the groups were the same at baseline.

NOTES

This review is partially replacing another review published under the title 'Inhaled bronchodilators for cystic fibrosis' ([Halfhide 2005](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenergic beta-2 Receptor Agonists [administration & dosage] [*therapeutic use]; Bronchodilator Agents [administration & dosage] [*therapeutic use]; Cystic Fibrosis [*drug therapy]; Disease Progression; Forced Expiratory Volume [drug effects]; Muscarinic Antagonists [administration & dosage] [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Time Factors; Tiotropium Bromide [administration & dosage] [*therapeutic use]

MeSH check words

Humans